2010 Annual Report: Cell Fate

News at CIRM

Taking Control of Cell Fate

Between a dish of stem cells and hope for a cure stands the pesky problem of turning those stem cells into a therapeutic cell type—a retina for eye disease, or a pancreatic cell for diabetes. Research this past year has shown that adult cells may change their identities, cell transplants can be made safer and someday the blind may see, thanks to advances CIRM scientists throughout California have made in controlling stem cell fate.

Career Switch

Dogma once held that if a cell was a doctor it would need to go back to kindergarten before it could grow up to become a lawyer: An adult cell needed to be reprogrammed back to an embryonic-like state, and from there, these so-called iPS cells would then be shepherded to a new adult fate.

That changed in 2009 when Harvard Stem Cell Institute researchers successfully converted one type of mouse pancreatic cell directly into insulin-pumping pancreatic beta cells. Cellular doctors, it turned out, could become lawyers after all.

2010 brought several additional cellular career switches, including one by Stanford scientist Marius Wernig, a CIRM grantee, who turned skin cells into nerve cells.

Later in the year, CIRM grantee Deepak Srivastava, director of the Gladstone Institute of Cardiovascular Disease at the University of California, San Francisco, coaxed mouse cardiac fibroblasts, the heart's support cells, to turn directly into primitive heart muscle cells. The research appeared in the August issue of Cell.

Srivastava's heart cell research could have important implications for the treatment of heart failure.

"Half of the cells in the heart are fibroblasts, so the ability to call upon this reservoir of cells already in the organ to become beating heart cells has tremendous promise for cardiac regeneration," Srivastava said. Nearly 6 million Americans suffer from heart failure because the heart is unable to repair itself after a heart attack, but only 2,000 hearts become available for transplanting each year.

Understanding Autism

In May 2009, CIRM held a workshop in which leading scientists discussed ways in which stem cell research could benefit people with autism. A key recommendation came to pass this year when CIRM grantees at the Salk Institute for Biological Studies were able to study neurons predisposed to autism spectrum disorders.

The team took skin cells from people with a genetic form of autism called Rett's syndrome, reprogrammed those back to iPS cells, and matured those embryonic-like cells into neurons. The unusual neurons that resulted provided scientists with a first glimpse of what makes an autistic neuron different. They had smaller cell bodies and fewer connections between neurons.

"Being able to study Rett neurons in a dish allows us to identify subtle alterations in the functionality of the neuronal circuitry that we never had access to before," said lead author Fred Gage, a professor in the Salk's Laboratory of Genetics.

The team took the work an additional step, exposing those scrappy neurons to an experimental drug and thereby reversing some abnormalities. Now they hope to study neurons developed from people with other forms of autism to start understanding the full spectrum of symptoms.

Scene of the Crime

Adult neural stem cells take advantage of the body's 911 system when they rush to the scene of damage in mouse models of multiple sclerosis. Once in place, the cells take on a mature fate.

Thomas Lane, an investigator at the Sue & Bill Gross Stem Cell Research Center at the University of California, Irvine, discovered the interactions that help stem cells home in on damage in research published in the P*roceedings of the National Academy of Science*. Lane, a CIRM grantee, earlier showed that adult neural stem cells improved motor function in mice with multiple sclerosis.

MS destroys myelin, the insulating sheath that covers nerves. Intact, myelin allows signals to propagate along the nerve; when damaged, signaling is interrupted.

When myelin corrodes, Lane discovered, inflammatory cells activate receptors on neural stem cells. Those stem cell receptors recruit protein guides called chemokines, which lead them to the accident and guide the stem cell's eventual fate. As the stem cells travel through the central nervous system, they begin to differentiate.

They reach the repair site in the form of oligodendrocyte precursor cells and finish maturing onsite. Three weeks after a stem cell treatment initiates, the cells are mature.

"In this study, we've taken an important step by showing the navigational cues in an inflammatory environment like MS that guide stem cells," said Lane. "Hopefully, these cues can be incorporated into stem cell–based treatments to enhance their ability to repair injury."
